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10/517,774	10/13/2005	Didier Montarras	263955US0XPCT	6948

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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/517,774	MONTARRAS ET AL.	
	Examiner	Art Unit	
	Scott D. Long	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks and Claim amendments, filed on 1 May 2008.

Claim Status

Claims 1-12 are pending. Claims 1, 2, 5 and 6 are amended. Claims 1-12 are under current examination.

Priority

This application claims benefit as a 371 of PCT/FR03/02010 (filed 6/27/2003). The application also claims benefit from foreign application CANADA 2391638 (filed 6/28/2002). The instant application has been granted the benefit date, 28 June 2002, from the application CANADA 2391638.

Response to Arguments - Claim Rejections 35 USC § 112

Response to Arguments – 35 USC 112, second paragraph

Applicant's arguments (Remarks, page 5) and Claim amendments, filed 1 May 2008, with respect to claims 1-12 have been fully considered and are persuasive. The applicant has incorporated "excluding in vitro expansion of said stem cells" into amended claim 1. The specification has support for this limitation on page 8, lines 13-14. Claim 2 is clarified by amendment. The rejections of Claims 1-12 under 35 USC 112, second paragraph, have been made moot by the claim amendments submitted on 1 May 2008 and are hereby withdrawn.

Response to Arguments - Claim Rejections 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Applicant's arguments (Remarks, pages 5-6) and claim amendments filed 1 May 2008 regarding the rejection of claims 1-12 under 35 USC 102(b) as anticipated by Okarma et al. (US-6143508) have been fully considered and they are persuasive.

The applicant has amended the claims so that it is clear that both mechanical dissociation AND enzymatic dissociation are required limitations of the instant claims. Furthermore, the applicant has argued that Okarma et al. teaches "mechanical OR enzymatic dissociation." The examiner finds this argument persuasive.

Therefore, the examiner hereby withdraws the rejection of claims 1-12 under 35 USC 102(b) as anticipated by Okarma et al. (US-6143508).

Applicant's arguments (Remarks, pages 6-7) and claim amendments filed 1 May 2008 regarding the rejection of claims 1, 3-4 and 6-9 under 35 USC 102(b) as anticipated by Mignone et al. (WO2001/36482) have been fully considered but they are only partially persuasive.

The applicant argues Mignone does not describe maintaining cells in a specific culture medium for preserving diversity and plasticity of the stem cells. Contrary to the applicant's assertion, Mignone et al. describe a method for preparing stem cells, in

which (mouse) brain was dissected out of the cranium and placed in $HBSS^{-/-}$ (page 28, line 27) after which trypsin was added and allowed to enzymatically digest the tissue, followed by triturating with a pipette until they were single cells (page 29, lines 2-4) and then the cells were resuspended in M21 serum free media and supplemented with EGF (page 29, lines 6-7). The resulting cells were maintained until later plated on laminin in the presence of FBS, after which "differentiation of various other cells types...were obtained" (page 29, lines 10-14). The M21 serum-free media supplemented with EGF as taught by Mignone et al. satisfy the limitation of claim 1 directed to "maintaining cells in a specific culture medium for preserving diversity and plasticity of the stem cells."

While the "M21 serum-free media supplemented with EGF" teaches a basic nutritive medium and a differentiation inhibiting factor, it does not seem to comprise a protective factor and hormones. Therefore, the examiner does not believe Mignone et al. satisfy the limitation of newly amended claims 6, 8 and 9. Accordingly, the examiner withdraws the rejection of claims 6, 8, and 9 as anticipated by Mignone et al.

However, the examiner hereby maintains the rejection of claims 1, 3-4 and 7 under 35 USC 102(b) as anticipated by Mignone et al. (WO2001/36482).

Applicant's arguments (Remarks, pages 6-7) and claim amendments filed 1 May 2008 regarding the rejection of claims 1 and 3-9 under 35 USC 102(b) as anticipated by DiMario et al. (Experimental Cell Research. 1995. Vol.216, No.2: 431-442) have been fully considered but they are only partially persuasive.

The applicant argues that DiMario et al. do not describe any step corresponding to the 4th step of claim 1 directed to "maintaining cells in a specific culture medium for preserving diversity and plasticity of the stem cells." Further, the applicant asserts that DiMario et al teach that cells cannot be maintained in a cell culture medium without losing their plasticity and diversity.

Contrary to the applicant's assertions, DiMario teach "maintaining cells in a specific culture medium for preserving diversity and plasticity of the stem cells." For example, DiMario et al. teach isolated myoblast cells were maintained in culture media containing horse serum, bFGF (differentiation inhibiting factor), are collected by means of filtration, then stored in Hank's Buffered Salt Solution (HBSS) before being injected into a chicken embryo hindlimb buds (page 433, col.1, Cell Transplantation). DiMario et al. indicate that "over time, a portion of the myoblasts maintained in vitro irreversibly differentiate before injection." (page 441, lines 25-26). Although some portion of the myoblasts differentiated so that they no longer the plasticity of stem cells, another portion of the myoblasts did not irreversibly differentiate before injection. DiMario et al. teach "myoblasts which still retain high myogenic potential throughout the cell culture period and which are maintained in the cell cycle by culture conditions promptly differentiate into muscle fibers when removed from the cell culture environment." (page 441, col.1, bottom parag.). Therefore, the examiner believes that DiMario et al. at least teach the minimal limitations of claim 1, 3, 7. The limitation of amended claims 5-6, and 8-9 requiring that the culture medium is devoid of animal serum is not anticipated by DiMario et al. Since the tissue regenerated by transplantation in DiMario et al. is

muscle tissue, the examiner believes claim 4 is not taught by DiMario et al. Therefore, the rejections of claims 4-6 and 8-9 as anticipated by DiMario et al. are hereby withdrawn.

However, the examiner hereby maintains the rejection of claims 1, 3 and 7 under 35 USC 102(b) as anticipated by DiMario et al.

Applicant's arguments (Remarks, page 8) and claim amendments filed 1 May 2008 regarding the rejection of claims 1 and 3-9 under 35 USC 102(b) as anticipated by Pouzet et al. (Circulation. 2000. Vol.102, No.19: III-210-III.215) have been fully considered and they are persuasive.

While the examiner disagrees with the particular argument put forth by the applicant, regarding the preservation of diversity and plasticity of stem cells cultured in the medium described by Pouzet et al., the examiner has determined that the new limitation introduced into claim 1, regarding "excluding in vitro expansion of said stem cells" is sufficient to overcome the Anticipation rejection. The stem cells isolated by Pouzet et al. are expanded in vitro prior to transplantation.

Therefore, the examiner hereby withdraws the rejection of claims 1 and 3-9 under 35 USC 102(b) as anticipated by Pouzet et al.

Response to Arguments - Claim Rejections 35 USC § 103

Applicant's arguments (Remarks, pages 9-10) and claim amendments filed 1 May 2008 regarding the rejection of claims 1-12 under 35 USC 103(a) as obvious over Pouzet et al. (Circulation. 2000. Vol.102, No.19: III-210-III.215) in view of DiMario et al. (Experimental Cell Research. 1995. Vol.216, No.2: 431-442) have been fully considered and they are persuasive.

The applicant argues that Pouzet et al. teach away from maintaining cells as in the claims because Pouzet et al. teaches in vitro expansion of stem cells for transplantation. The examiner wholeheartedly disagrees with the applicant's characterization that "Pouzet makes it clear that in vitro expansion is mandatory for skeletal myoblast transplantation to be effective" (Remarks, page 9, parag.2). Rather, Pouzet hypothesize that the failure of the "mincing group" cells is due to the relative lack of myoblasts in the tissue chunks transplanted; Pouzet et al. state, "This hypothesis is supported by recent unpublished data of our laboratory showing that postransplantation functional outcome is linearly related to the number of injected myoblasts" (page III-215, col.1, parag. 1). The examiner finds the applicant's mischaracterization of the teachings of Pouzet et al. to be unnecessary and inappropriate. The strongest argument for "teaching away" is that Pouzet suggests that a large number of transplanted myoblasts is required for function recovery, while DiMario teach that their culture methods do not produce a large number of myoblasts. In light of the amendment directed to "excluding expansion of stem cells," the examiner believes a skilled artisan would not combine the prior art to make the instant invention.

Therefore, the examiner hereby withdraws the rejection of claims 1-12 under 35 USC 103(a) as obvious over Pouzet et al. in view of DiMario et al.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-12 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Reid et al. (US-6,069,005, issued May 30, 2000).

Claim 1 is directed to a method for preparing human or animal stem cells, said method comprising: cell extraction; mechanical dissociation; enzymatic dissociation; and maintaining of the cells obtained, in a specific culture medium for preserving diversity and plasticity of the stem cells, said method excluding in vitro expansion of said stem cells. Reid et al. teaches methods of isolating hepatoblasts. Reid et al. teaches "cells from day 15 gestation livers were panned against rat red blood cells antibody and the epithelial-enriched cell suspension was plated in a serum-free hormonally defined medium with αMEM as a basal medium" (col.15, lines 47-50). Reid et al. also teach, "in order to isolate fetal liver cells, pregnant rats at the fourteenth day of gestation were euthanized...livers were then dissected from the fetuses...livers were moved to a 50 ml conical centrifuge tube by pipette, gently triturated 6 to 8 times to partially disaggregate the tissue...tissue was resuspended in50 ml 0.6% collagenase D...gently triturated...cells suspension was centrifuged and the cells were resuspended in ...HBSS-MEM" (col.7, line 54 to col.8, line 16). Reid et al. also teach, "cells before and after sorting were maintained at 4oC and in HBSS-MEM." (col.8, line 55). According to the examiner's reading of Reid et al., the cells were not expanded or differentiated while being maintained in the culture medium.

Claim 2 is directed to the method of claim 1, wherein the culture media comprises at least a) a nutritive medium; b) a protective factor; c) hormones; and d)

differentiation inhibiting factors. The specification indicates that a "protective factor" can be transferrin (page 9, line 4). The specification indicates that a "hormone" can be insulin (page 9, line 6). The specification indicates that a "differentiation inhibiting factor" can be EGF (page 9, line 17). Reid et al. teach that their minimal essential medium (MEM) can contain transferrin, insulin, and EGF (col.8, line 9 and col. 9, lines 18, 22).

Claim 3 is directed to the method of claim 1 wherein said stem cells are animal or human stem cells selected form the group consisting of progenitor stem cells for a tissue. Reid et al. teach methods of isolating hepatoblasts.

Claim 4 is directed to the method of claim 3, wherein the tissue is selected from the group consisting of skin, liver, heart, bone, and nerve tissues. Reid et al. teach methods of isolating hepatoblasts.

Claim 5 is directed to a medicinal product comprising the human or animal stem cells, obtained according to the method of claim 1, and one or more additives comprising a specific culture medium devoid of animal serum, the culture medium comprising a) a nutritive medium; b) a protective factor; c) hormones; and d) differentiation inhibiting factors. Reid et al. teach isolated hepatoblasts in MEM comprising transferrin, EGF and insulin. (col.8 , line 9 and col. 9, lines 18, 22).

Claim 6 is directed to a stem cell obtained according to the method of claim 1 which is in a specific culture medium devoid of animal serum, the culture medium comprising a) a nutritive medium; b) a protective factor; c) hormones; and d)

differentiation inhibiting factors. Reid et al. teach isolated hepatoblasts in MEM comprising transferrin, EGF and insulin. (col.8 , line 9 and col. 9, lines 18, 22).

Claim 7 is directed to a method of treatment comprising implanting autologous or heterologous animal stem cells, obtained according to the method of claim 1. Reid et al. teach "this invention is further directed to use of hepatoblasts…to treat liver dysfunction…liver transplantation." (col.7, lines 26-32).

Claim 8 is directed to a cell composition comprising human or animal stem cells, obtained according to the method of claim 1; a specific culture medium devoid of animal serum, the culture medium comprising a) a nutritive medium; b) a protective factor; c) hormones; and d) differentiation inhibiting factors. Reid et al. teach isolated hepatoblasts in MEM comprising transferrin, EGF and insulin. (col.8 , line 9 and col. 9, lines 18, 22).

Claim 9 is directed to the composition of claim 8, wherein the stem cells have the ability to colonize and the ability to allow functional recovery. Reid et al. teach "hepatoblasts can be injected into the body, such as into the liver or into an ectopic site" (ocl.7, lines 30-31).

Claim 10 is directed to a method of treating disease by cell therapy or gene therapy, comprising, injecting the human or animal stem cells, obtained by the method of claim 1, into a subject in need thereof. Reid et al. teach, "further, hepatoblasts can be used in gene therapy" (col.7, line 38).

Claim 11 is directed to the method for preparing stem cells as claimed in claim 2, wherein said stem cells are animal or human stem cells selected from the group

consisting of progenitor stem cells for a tissue. Reid et al. teach methods of isolating hepatoblasts.

Claim 12 is directed to the method as claimed in claim 11, wherein the tissue is selected from the group consisting of skin, liver, heart, bone, and nerve tissues. Reid et al. teach methods of isolating hepatoblasts from liver.

Accordingly, Reid et al. anticipated or is obvious over the instant claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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